composition comprising, per milliliter thereof, between about 0.05 and about 500 NIH units of thrombin and also, per milliliter, between about 5 and about 30 mg of a fibrinogen composition wherein clottable fibrinogen is recovered from a process comprising precipitating fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol 1000 and reprecipitating said fibrinogen with glycine, wherein precipitation of said fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in said sample is recovered, said recovered fibrinogen capable of being polymerized to a fibrin network having therapeutically effective strength, when present at said site at a concentration of about 30 mg/ml or less; wherein about 95%, or greater, of total protein present in said fibrinogen composition is fibrinogen.

Remarks

This Amendment addresses the Office Action dated October 11, 2001. Accordingly, reconsideration and allowance of the subject application is respectfully requested.

Applicants initially note that the Office Action indicates that claims 1-14 and 18-37 are pending in the subject application, of which claims 18-37 have been withdrawn as a result of a restriction requirement. However, Applicants previously elected Group I, claims 1-14, *26 and 35-37*. Correction is respectfully requested.

In the afore-referenced Action, claims 1-14 were rejected under 35 U.S.C. § 112 for allegedly being indefinite and failing to further limit the subject matter of a previous claim. Applicants respectfully traverse this rejection. However, in the interest of advancing the prosecution of the application, the composition of independent claims 1, 2 and 13 has been clarified. Accordingly, withdrawal of these rejections is believed to be warranted.

Claims 1-11 and 13 were then rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,377,572 to Schwarz et al. ("Schwarz") in view of WO 92/13495 to Tripodi ("Tripodi"). Applicants respectfully assert that the present claims and remarks obviate these rejections.

Applicants claims are directed to therapeutic compositions of high fibrinogen yield and therapeutically effective strength. For example, independent claim 1 specifies that about 95%, or greater, of the total protein present in the composition is fibrinogen, and independent claim 2 specifies that the composition contains less than about 30% of proteins other than fibrinogen. Similarly, independent claim 13 is directed to a reactive therapeutic composition of thrombin and fibrinogen composition. This claim also specifies that about 95%, or greater, of the total protein present in the fibrinogen composition is fibrinogen.

Applicants' claims further specify, in part, that the fibrinogen is obtained from precipitating fibrinogen from a sample of non-human mammalian blood plasma with polyethylene glycol 1000 and reprecipitating the fibrinogen with glycine, wherein precipitation of the fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in the sample is recovered. *See* page 26 of Applicants' specification.

As disclosed in Applicants' specification at page 27, precipitation of fibrinogen with PEG 1000 leads to a cohesive fibrinogen precipitate that is more readily collected, for resuspension, than fibrinogen precipitate resulting from contact with, for example, PEG 8000. Accordingly, use of low molecular weight PEG (such as PEG 1000) facilitates recovery of clottable fibrinogen.

Referring now to the Schwarz reference cited by the Examiner, it is respectfully asserted that this reference does not disclose nor suggest Applicants' presently claimed invention. For example, the tissue adhesive of Schwarz includes

fibrinogen in an amount of at least 70 mg/ml (Col. 1, lines 57-61). As distinguished in Applicants' specification at page 4, line 21 continuing to page 5, line 19:

> [t]herapeutic adhesive fibrinogen compositions disclosed [in Schwarz] are stated to require concentrations of fibrinogen of at least about 70 mg/ml (which may again be diluted 1:1 at the treatment site by contact with a thrombin-containing solution).
>
> The present invention relates to fibrinogen-containing compositions that have *surprising clinical (medical) utility* as adhesives, sealants, or hemostatic agents, and that provide therapeutically effective strength at fibrinogen concentrations at the treatment site of, for example, *only about 10 mg/ml. The more dilute and less viscous nature of the therapeutic compositions provided according to the practice of the present invention decreases substantially the time necessary to resuspend such compositions from the lyophilized form, an important advantage in, for example, the hospital emergency room. Filtration of the fibrinogen during processing is also facilitated.*

Thus, the tissue adhesive of Schwarz appears to even teach away from the present invention.

It is respectfully asserted that the addition of Tripodi does not cure the shortcomings of Schwartz. Tripodi is directed to a fibrinogen based adhesive. However, in contrast to Applicants' claimed invention, Tripodi recommends the use of PEG-8000 (Page 6). In further contrast to Applicants' claimed invention, Tripodi teaches that the "PEG precipitation step may be repeated two or three times at a temperature which does not adversely affect the precipitation reaction..." (Page 6). Accordingly, it is respectfully asserted that Tripodi also teaches away from the present invention. In view of the foregoing, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-3, 7-11 and 13-14 were then rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,427,650 to Stroetmann ("Stroetmann '650") or U.S. Patent No. 4,442,655 to Stroetmann ("Stroetmann '655") in view of Tripodi. Similarly, Claims 1-3, 5, 7-11 and 13-14 were rejected under 35 U.S.C. §

103(a) as being obvious over Stroetmann '650 or Stroetmann '655 in view of Tripodi and further in view of the article, entitled, *The Measurement of Fibrino gen and its Derivatives* by Farrell et al. ("Farrell"). Applicants respectfully traverse these rejections.

In contrast to the present invention, Stroetmann '650 is directed to enriched plasma derivative for advancement of wound closure and healing, wherein the fibrinogen is isolated from *human plasma* (Col. 3, line 17, emphasis added). Specifically, Stroetmann '650 discloses that "it has been recognized according to the invention that the fibrinogen isolated from human plasma shall largely be free from cryo-insoluble globulin . . ." (Col. 3, lines 15-31).

However, in the presently claimed invention the fibrinogen is obtained from non-human mammals. As described in Applicants' specification at page 10, line 15 continuing to page 12, line 10 (emphasis added):

> [t]he therapeutic compositions of the invention comprise non-autologous, non-single donor mammalian fibrinogen . . . Preferred donors are mammals other than the human . . . Fibrinogen compositions that could be provided from mammalian species other than the human are disclosed, for example, in U.S. Patents No. 4,377,572 and 4,362,567. However, the therapeutic compositions defined therein *are stated to contain at least about 70 mg/ml or more of fibrinogen (prior to any dilution at the site of treatment) leading potentially to the presence also therein of a substantial amount of additional and antigenic protein impurities*, there resulting an associated risk of severe immune response. . .

Thus, Stroetmann '650 also appears to teach away from the presently claimed invention, as does Stroetmann '655. That is, Stroetmann '655 discloses that "[p]referably, a relatively high fibrinogen concentration of approx. 50-80 mg/ml is provided . . . Therefore, an increased fibrinogen concentration in the initial solution leads to a denser end product of higher mechanical strength" (Col. 4, lines 14-21).

It is respectfully asserted that the addition of Tripodi or Farrell does not cure the shortcomings of either Stroetmann '650 or '655. For example, Tripodi was cited by the Examiner as disclosing bovine plasma. However, for the reasons stated above, it is respectfully asserted that Tripodi does not cure the shortcomings of these references.

Farrell is a technical paper merely documenting the investigation of the minimal concentration of ε-amino caproic acid in plasma required to induce total suppression of *in vitro* fibrinogenolysis and fibrinolysis, as well as the effect this EACA concentration produced on recovery of thrombin clottable fibrinogen estimates. These results were compared with clot recovery from plasma to which either fibrin degradation products or fibrinogen degradation products had been added (*See*, page 328 of Farrell).

For the foregoing reasons, it is respectfully asserted that there is no teaching, suggestion or motivation in either Stroetmann '650, Stroetmann '655, Farrell or Tripodi that would lead one of ordinary skill in the art to combine and modify these references, and the Examiner has pointed to no such suggestion. Accordingly, in view of the foregoing amendments and remarks, withdrawal of the rejection is believed to be warranted.

Claims 1-11 and 13-14 were also rejected under 35 U.S.C. § 103(a) as being obvious over Stroetmann '650 or Stroetmann '655 in view of Tripodi, Farrell and U.S. Patent No. 5,116,950 to Miyano et al. ("Miyano").

The teachings of Stroetmann '650, Stroetmann '655, Tripodi and Farrell have been described above, and it is respectfully asserted that the addition of Miyano neither discloses nor suggests Applicants' presently claimed invention. For example, Miyano relates to a process for heat treating an aqueous solution containing fibrinogen to thereby inactivate virus(es) therein (Col. 1, lines 5-8). According to

Miyano, fibrinogen is frequently accompanied by a risk of contamination with virus(es), in particular, hepatitis or AIDS virus. Accordingly, it should be heated to inactivate these viruses. However, fibrinogen is unstable to heat and thus inactivated during the conventional liquid heating process. Accordingly, it has been desired to provide a process for heating fibrinogen to inactivate viruses contaminating the same without inactivating the fibrinogen per se (Col. 1, lines 28-36).

Thus, Miyano even addresses a problem distinct from that which is addressed and solved by the present invention and one skilled in the art would not even be motivate to look to Miyano for guidance, let alone combine this reference with the afore-cited references for the foregoing reasons. Withdrawal of this rejection is therefore believed to be warranted.

Lastly, independent claim 2 and 12 depending therefrom were rejected under 35 U.S.C. § 103(a) as being obvious over Stroetmann '655 in view of the abstract of *Preparation of Rat Fibrinogen* by Richter et al. ("Richter") and Tripodi.

It is respectfully asserted that the addition of Richter and Tripodi to Stroetmann '655 neither discloses nor suggests Applicants' presently claimed invention. Tripodi and Stroetmann '655 have been described above and the addition of Richter does not cure the shortcomings in the teachings of these references. For example, Richter merely is directed to the preparation of rat fibrinogen and a comparison of the intermediate, as well as final products, of rat fibrinogen with those of human fibrinogen (Abstract).

For the foregoing reasons, Applicants' presently claimed invention provides a useful and therapeutic composition that is neither anticipated nor rendered obvious by the afore-cited references, whether the references are viewed alone or in combination.

All issues raised by the Examiner having been addressed, it is respectfully submitted that the subject application is in condition for allowance.

The Examiner is invited to telephone the undersigned attorney at 212-425-7200 with any questions or comments regarding this Amendment.

Authorization is also hereby given to charge any deficiency in fees in connection with this Amendment to our Deposit Account No. 11-0600.

Also, attached hereto is a Marked-up Version Showing Changes Made By The Present Amendment in accordance with 37 C.F.R. § 1.121.

Respectfully submitted,

Date: 1/9/02

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Marked-up Version Showing Changes Made
By The Present Amendment (37 C.F.R. § 1.121)

In the Claims:

1. (Amended) A therapeutic composition [having a high yield of fibrinogen and being] effective on contact with thrombin at a site of treatment in a patient as a tissue adhesive, hemostat or sealant, said composition comprising non-autologous, non-single donor mammalian, clottable fibrinogen recovered from a process comprising precipitating fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol 1000 and reprecipitating said fibrinogen with glycine, wherein precipitation of said fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in said sample is recovered, wherein said recovered fibrinogen is capable of polymerizing when provided in solution at said site at a concentration of about 10 mg/ml thereof or less, to a fibrin network having therapeutically effective strength, and said composition further comprising a sufficient amount of one or more physiologically-compatible solutes such that said composition, if formulated as a lyophilized material, can be reconstituted therefrom at room temperature in sterile water for injection in about 30 minutes or less, at about 25 mg/ml of said fibrinogen[, said fibrinogen being made present at said site of treatment at a concentration of about 10 mg/ml or less];

wherein about 95%, or greater, of total protein present in said composition is fibrinogen.

2. (Amended) A therapeutic composition [having a high yield of fibrinogen and being] effective on contact with thrombin at a site of treatment in a patient as a tissue adhesive, hemostat or sealant, said composition comprising non-autologous, non-single donor mammalian, clottable fibrinogen recovered from a process comprising precipitating fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol 1000 and reprecipitating said fibrinogen with glycine, wherein precipitation of said fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in said sample is recovered, wherein said recovered fibrinogen is capable of polymerizing when provided in solution at said site at a concentration of about 30 mg/ml thereof or less, to a fibrin network having therapeutically effective strength, wherein said composition contains less than about 30% (w/w), based on total protein mass present therein, of proteins other than fibrinogen, and said composition further comprises a sufficient amount of one or more low molecular weight physiologically-compatible solutes such that said composition, if formulated as a lyophilized material, can be reconstituted therefrom at room temperature in sterile water for injection in about 30 minutes or less, at about 25 mg/ml of said fibrinogen[, said fibrinogen being made present at said site of treatment at a concentration of about 30 mg/ml or less].

13. (Amended) A reactive therapeutic composition [having a high yield of fibrinogen and being] effective on contact at a site of treatment in a patient as a tissue adhesive, hemostat or sealant, said composition comprising, per milliliter thereof, between about 0.05 and about 500 NIH units of thrombin and also, per milliliter, between about 5 and about 30 mg of a fibrinogen composition wherein clottable fibrinogen is recovered from a process comprising precipitating fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol 1000 and reprecipitating said fibrinogen with glycine, wherein precipitation of said fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in said sample is recovered, said recovered fibrinogen [being] capable of being polymerized to a fibrin network having therapeutically effective strength, when present at said site at a concentration of about 30 mg/ml or less; wherein about 95%, or greater, of total protein present in said fibrinogen composition is fibrinogen.